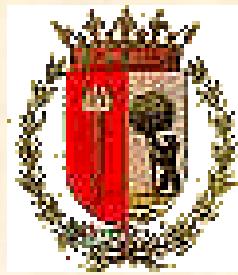


# **Taller 5. Función endotelial:**

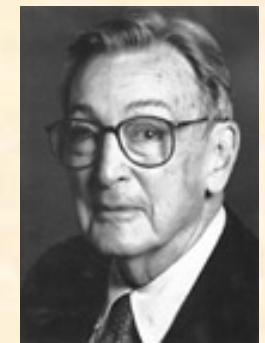
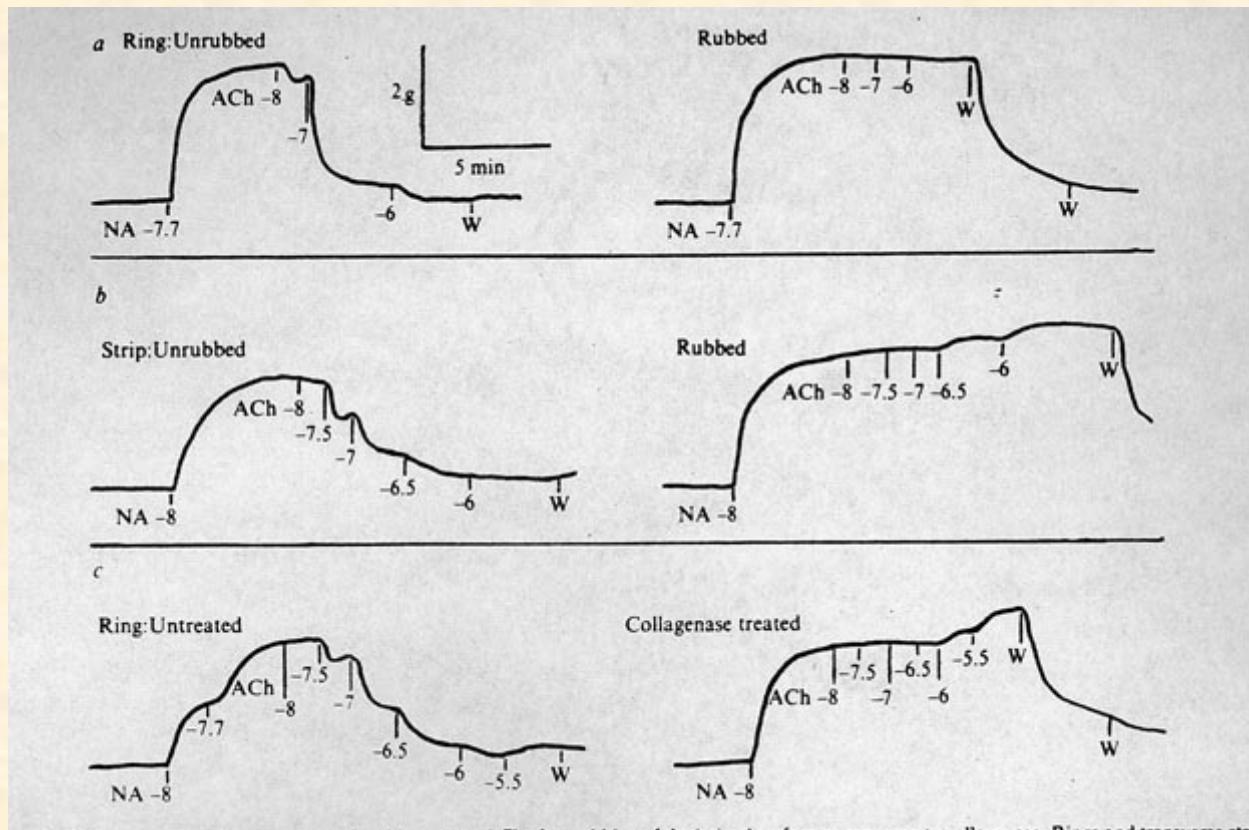
**Dr. Jorge F Gómez Cerezo. Servicio de Medicina Interna. Hospital Infanta Sofía**

## **1. El concepto de disfunción endotelial se refiere a:**

- 1. Una menor producción de óxido nítrico por el endotelio**
- 2. Una disminución de la vasodilatación dependiente de endotelio.**
- 3. Una menor respuesta a cualquier tipo de vasodilatador.**
- 4. Un aumento de las resistencias vasculares periféricas.**



# LIBERACION DE FACTORES VASOACTIVOS DEL ENDOTELIO VASCULAR: FUNCION ENDOTELIAL



R. Furchtgott  
Premio Nobel de  
Medicina 1998

Furchtgott and Zawadzki; Nature 288: 373-376, 1980

# DISFUNCION ENDOTELIAL

Dilataciones dependientes de endotelio

$\text{PGI}_2$

EDHF

NO

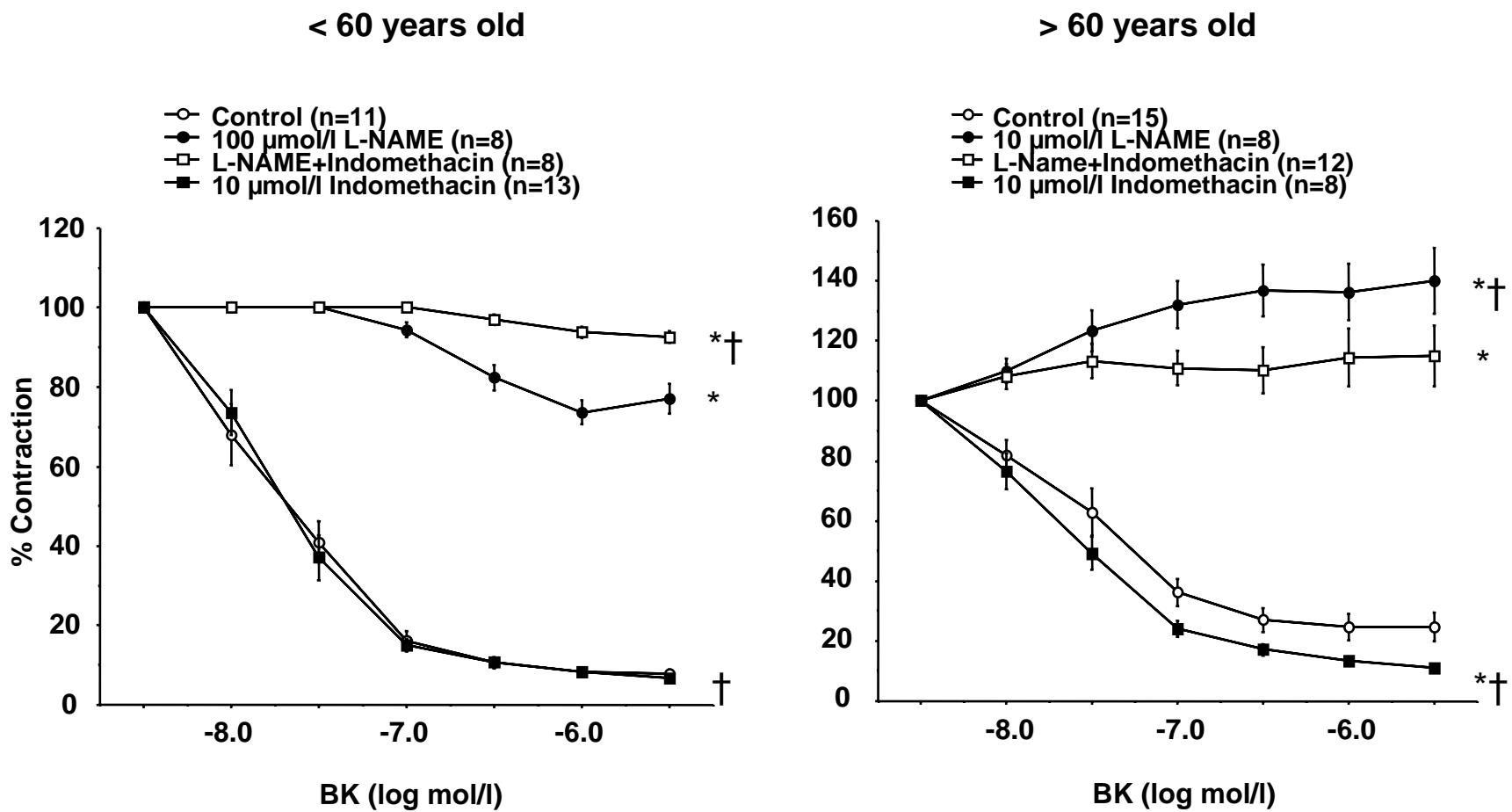
producción  
inactivación

Contracciones dependientes de endotelio

$\text{TXA}_2/\text{PGH}_2$

ET-1

$\text{O}^-_2$



**Figure 2**

Inflammation  
Vasoconstriction  
Platelet aggregation  
Procoagulant  
Proliferative

## Disease

- Ang II
- Endothelin
- Free radicals
- TXA<sub>2</sub>

## Health

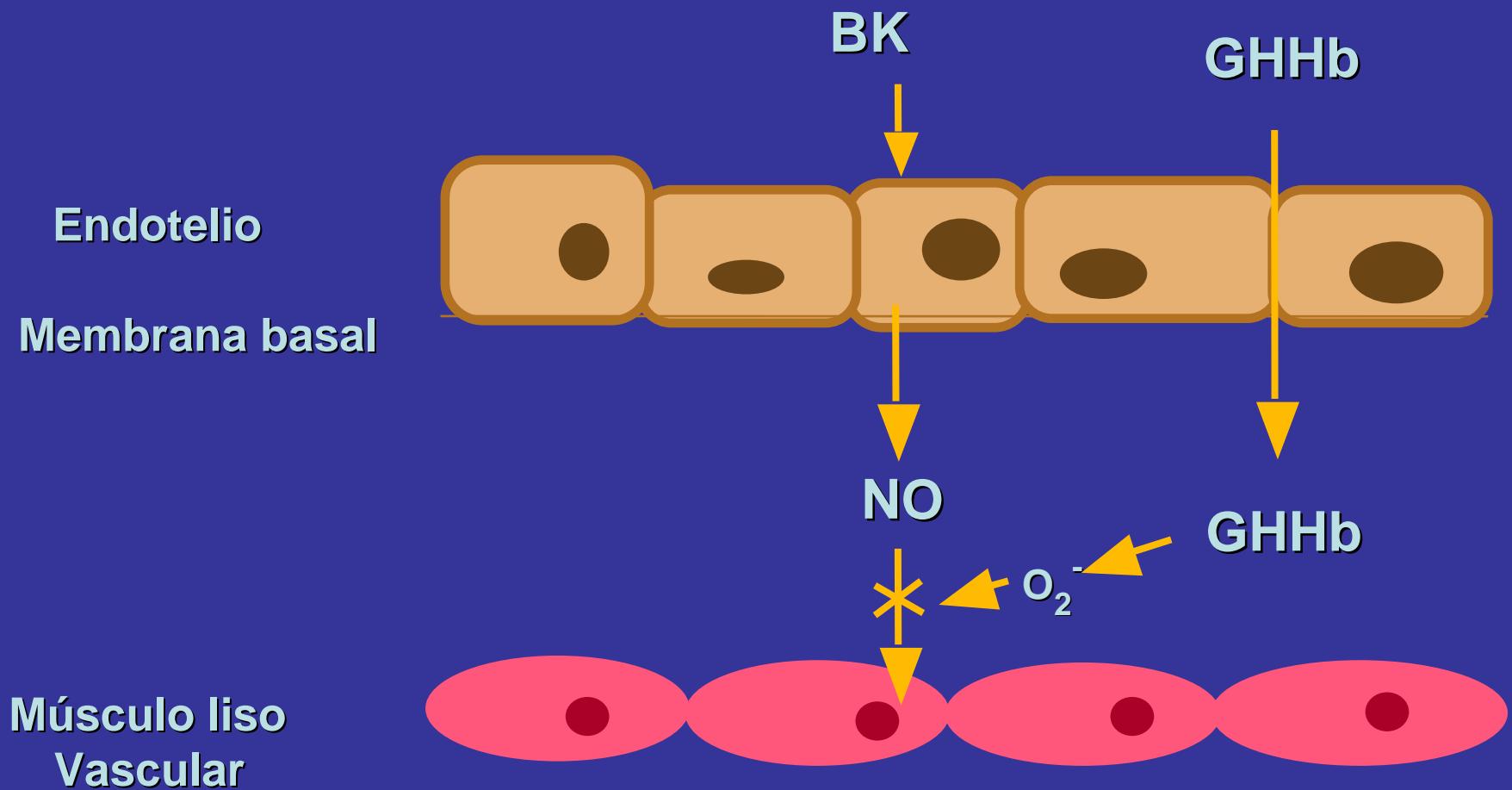
- Nitric Oxide
- PGI<sub>2</sub>
- EDHF

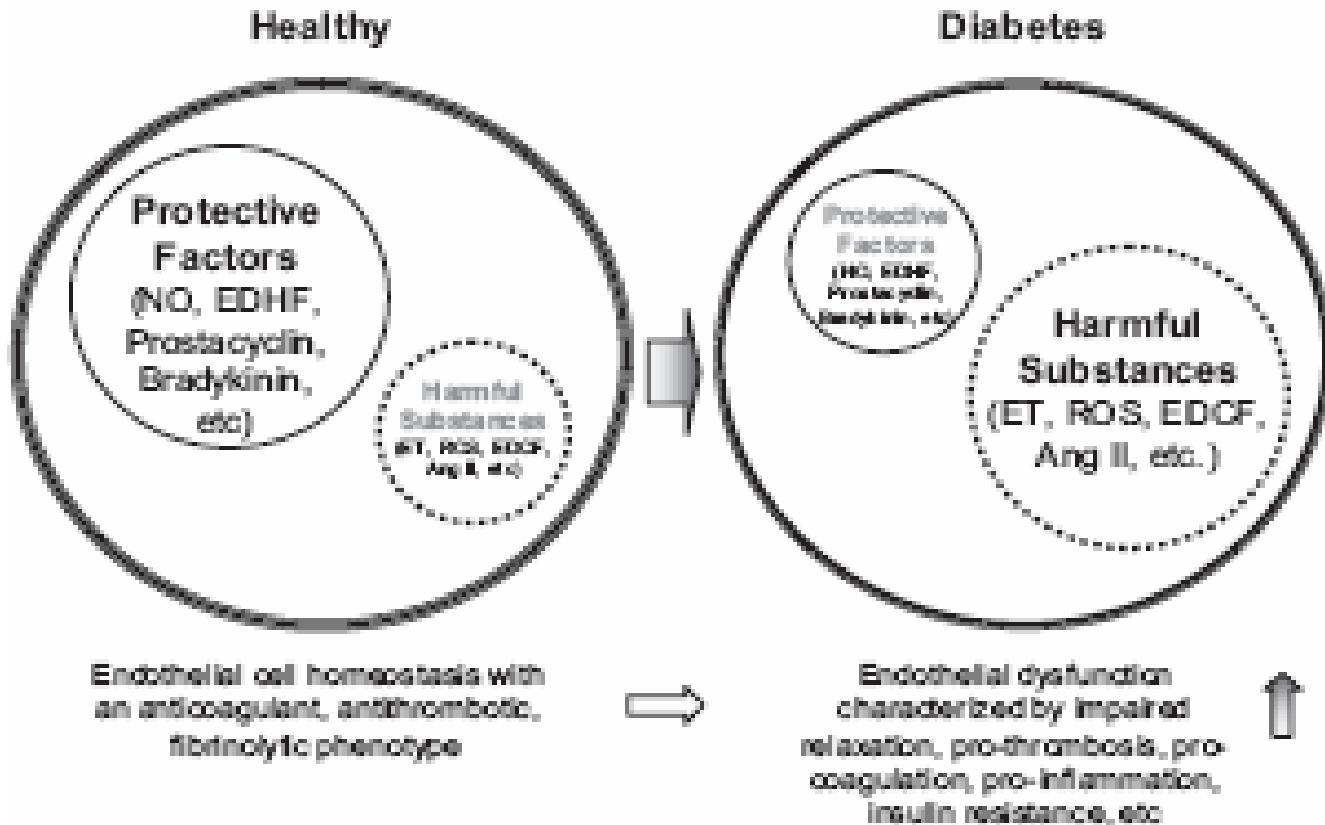
Antiplatelet  
Vasodilation  
Antiinflammatory  
Antiproliferative  
Fibrinolysis

Rodríguez-Mañas et al. Circulation 88: 2111-2116, 1993

Angulo et al. Hypertension 28: 583-592, 1996

Vallejo et al. Diabetologia 43: 83-90, 2000





# ***Taller 3. Función endotelial:***

## ***¿Cómo medirla?***

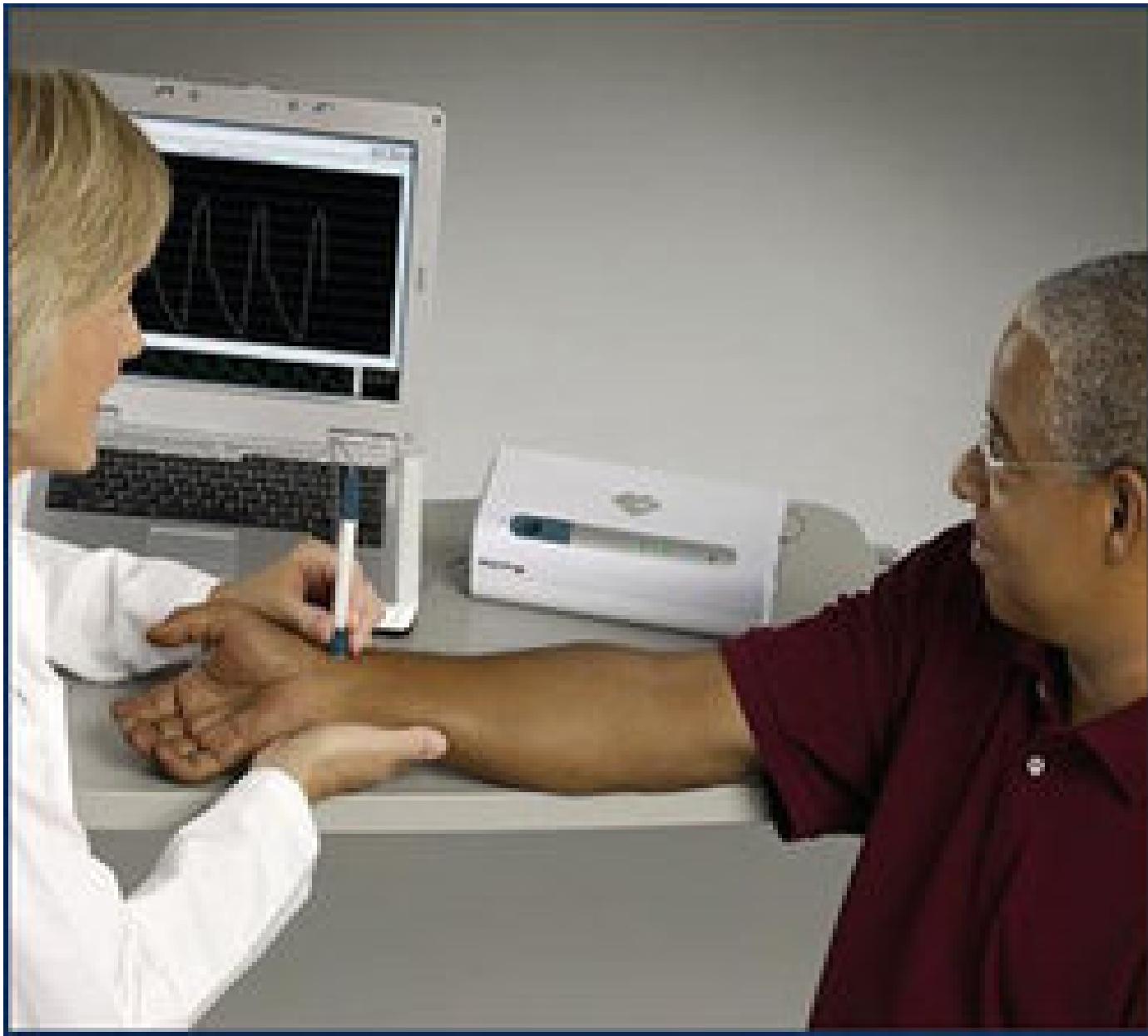
# **Summary of modalities for assessing endothelial function**

## **Microvasculature**

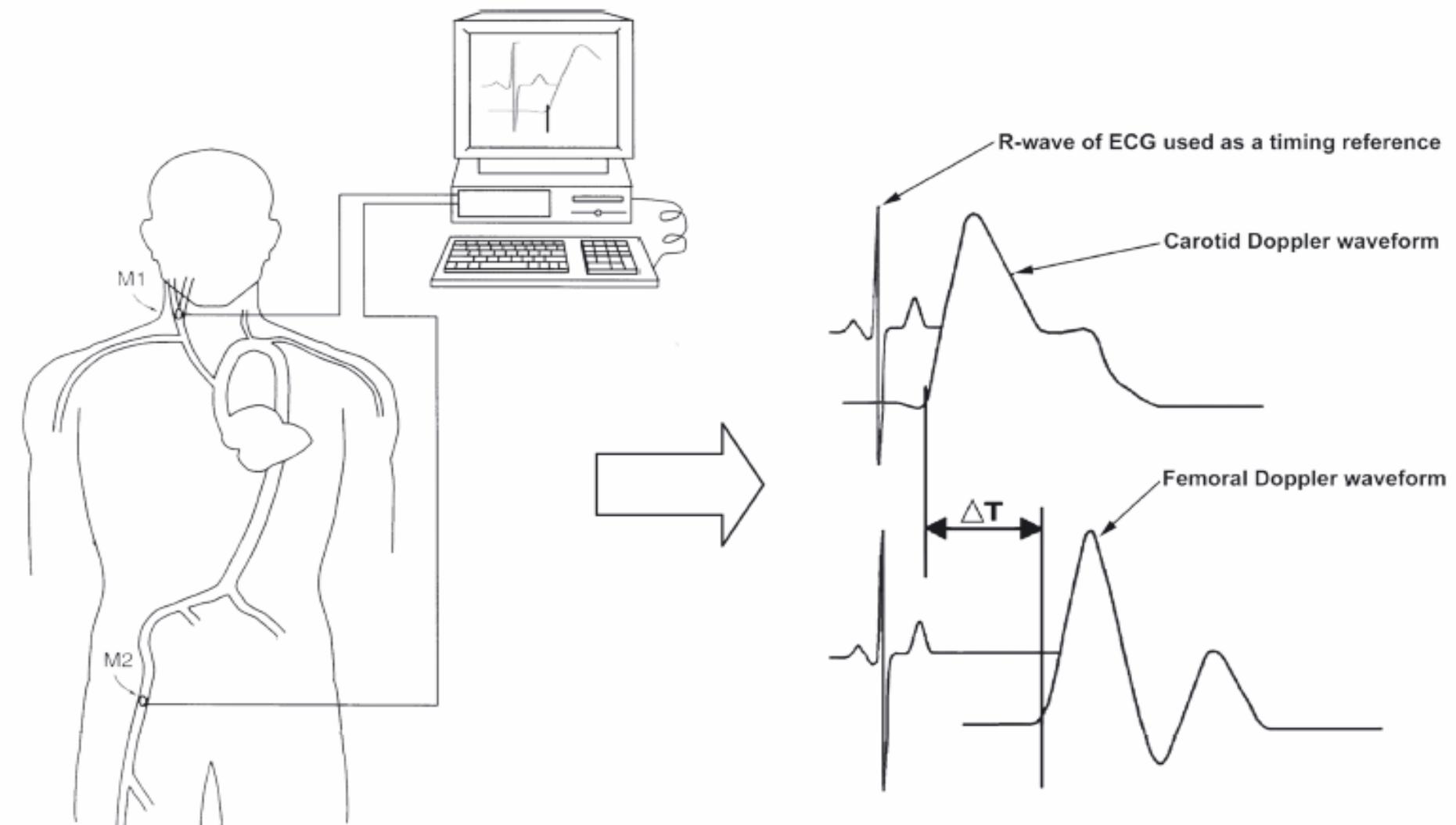
1. Pulse arterial tonometry
2. Coronary blood flow – Doppler
3. Coronary blood flow – positron emission tomography
4. Forearm impedance plethysmography
5. Pulse wave analysis (applanation tonometry)
6. Cardiac magnetic resonance
7. Laser Doppler flowmetry of the skin
8. Hyperemic velocity post occlusion

## **Conduit vessel**

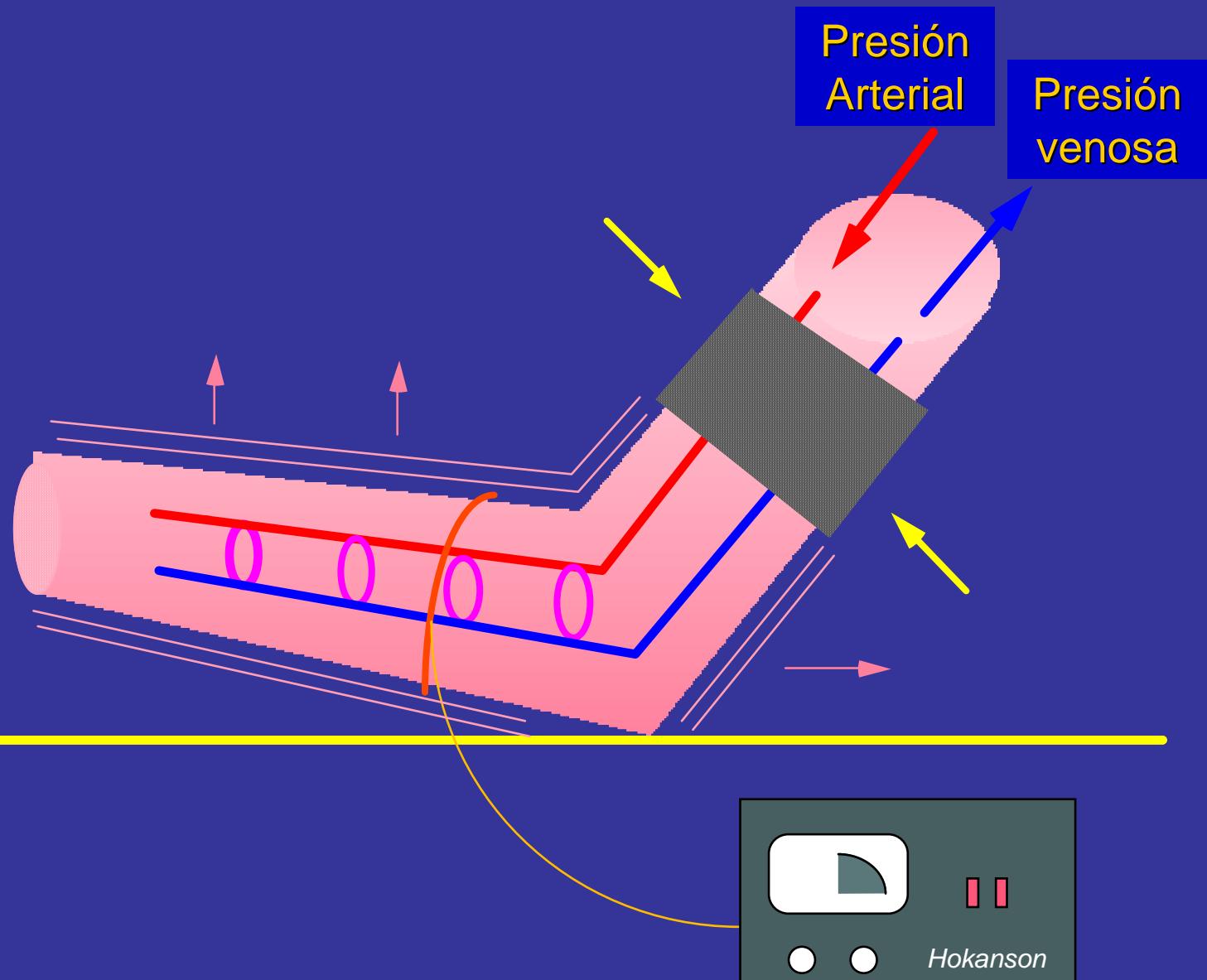
1. Flow-mediated dilation
2. Quantitative coronary angiography
3. Flow-mediated constriction



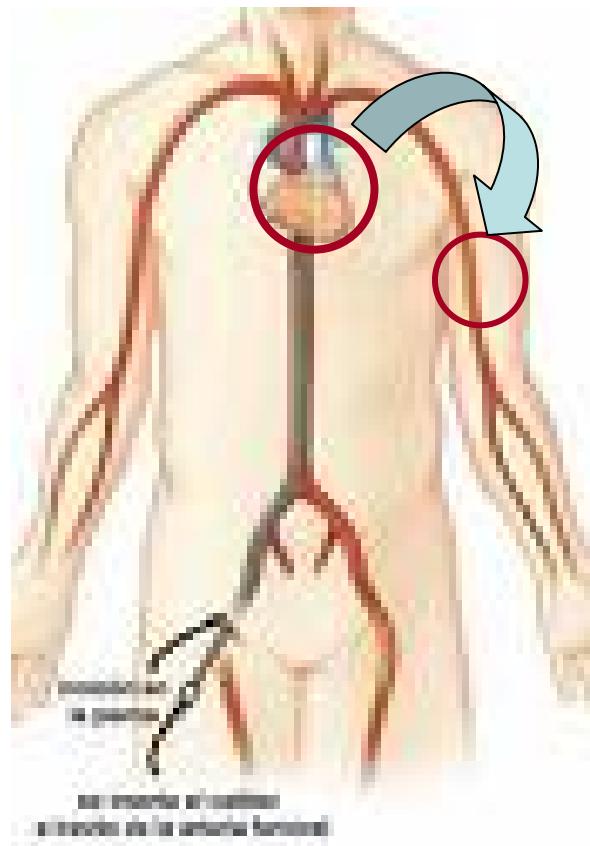
# VELOCIDAD DE LA ONDA DE PULSO

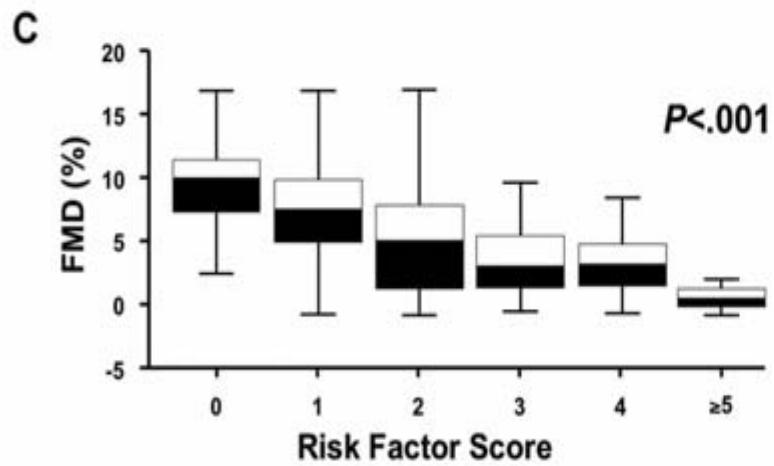
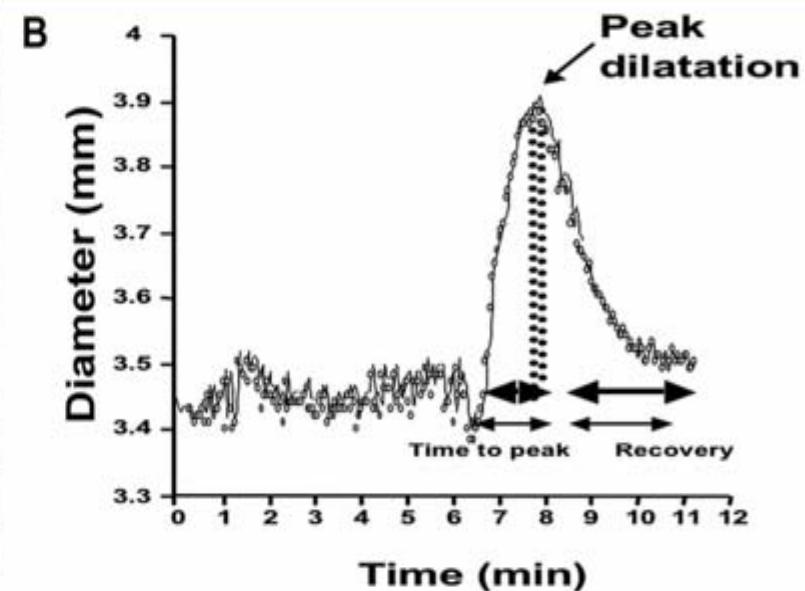
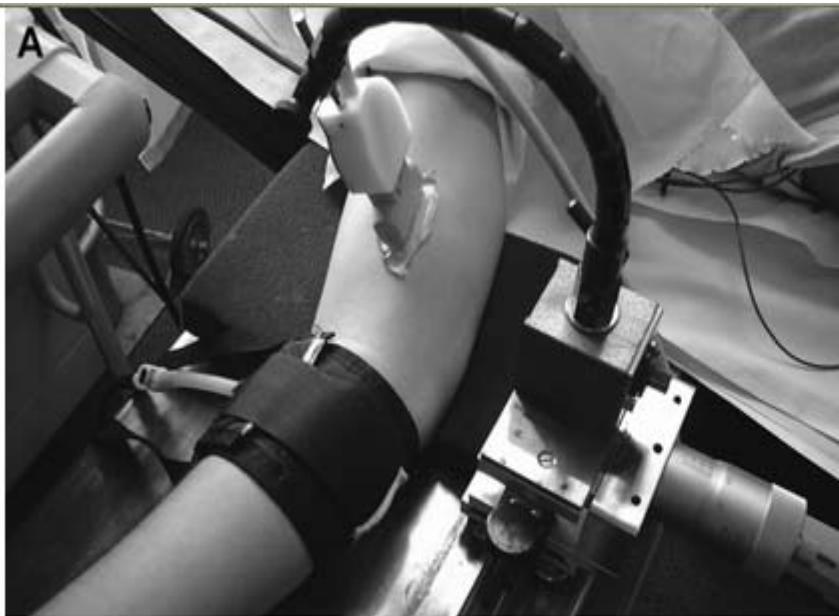




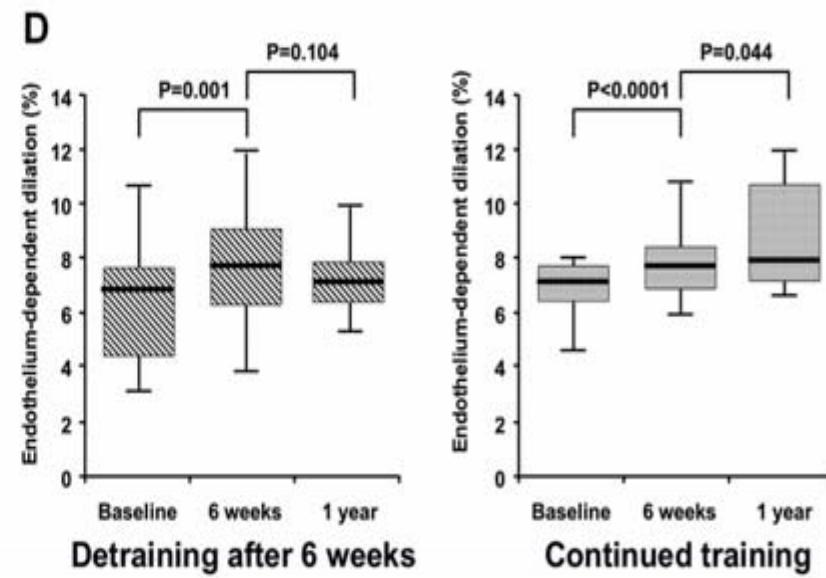


# DISFUCIÓN CORONARIA/BRAQUIAL





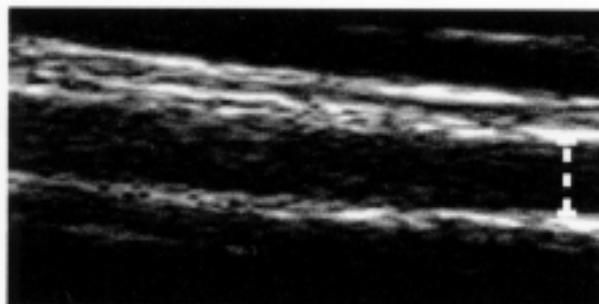
Cholesterol, smoking, mean blood pressure,  
family history, age, gender.



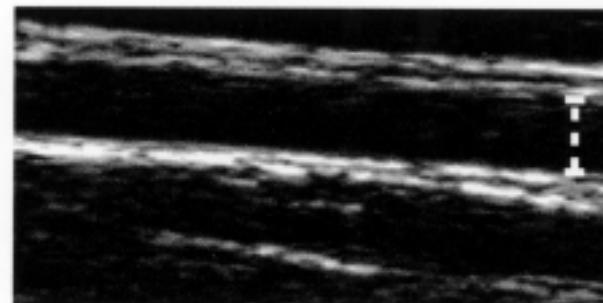
**Arteria braquial**

**A**

**basal**



**1 minuto**

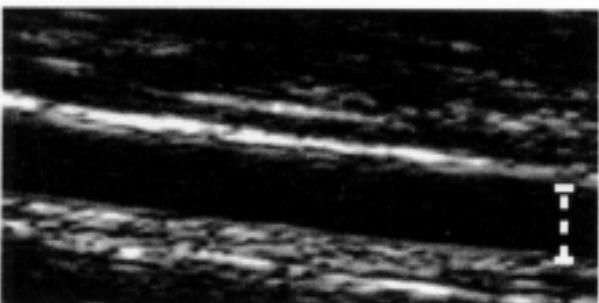


**2.5 mm**

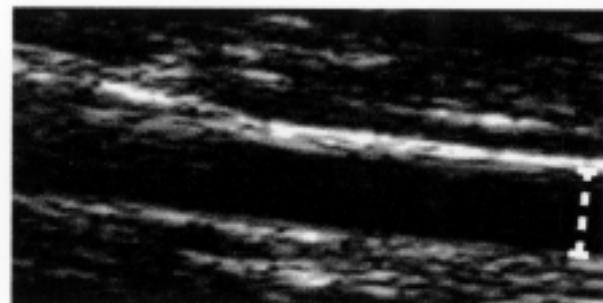
**2.6 mm**

**B**

**basal**



**1 minuto**

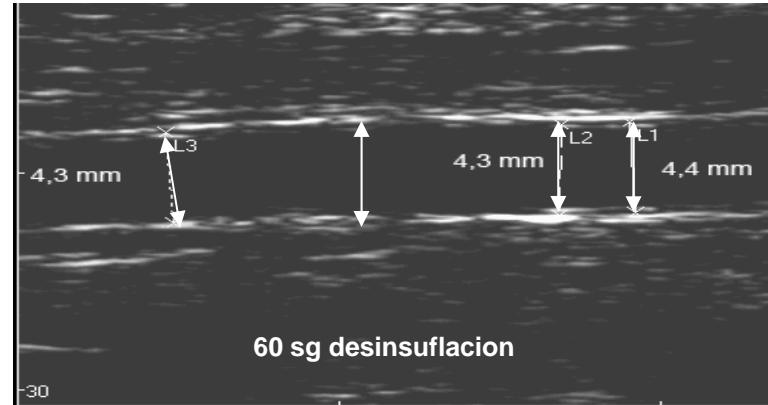
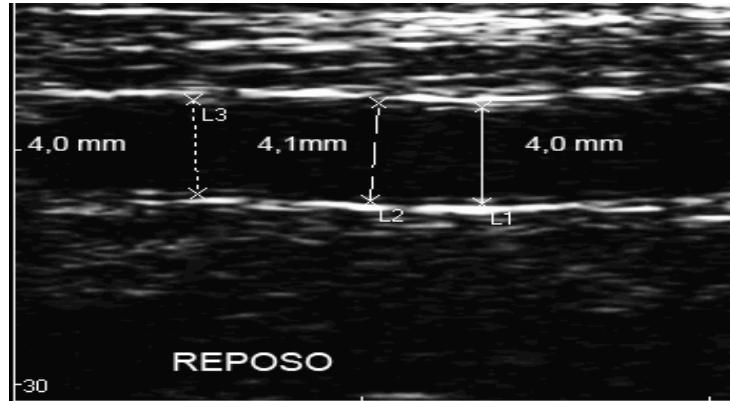


**2.5 mm**

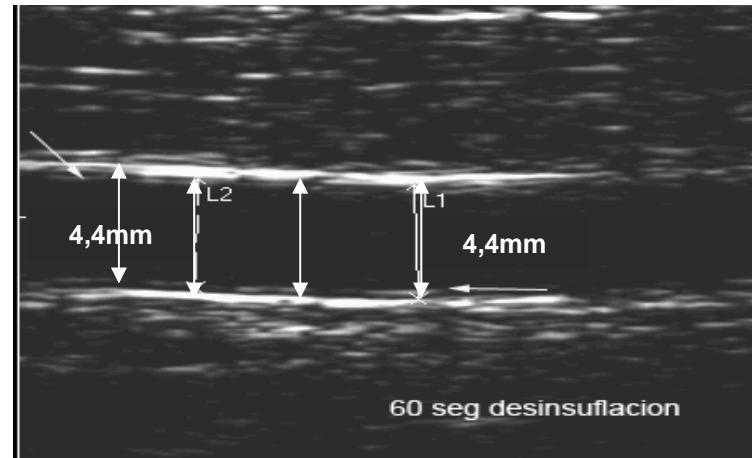
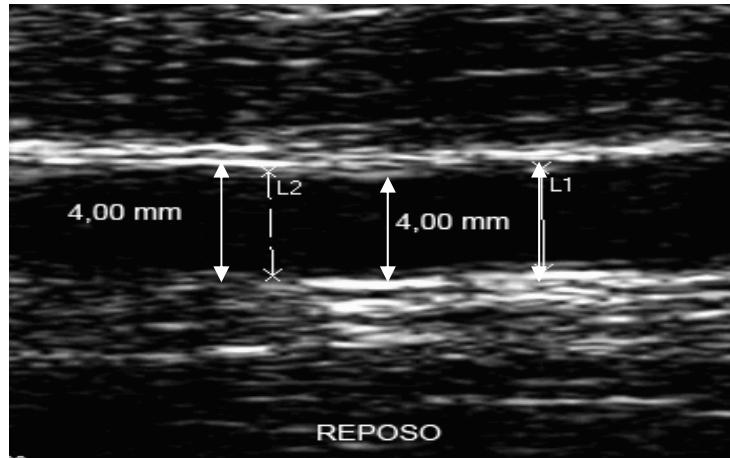
**2.8 mm**

# Función endotelial: protocolo

## Basal



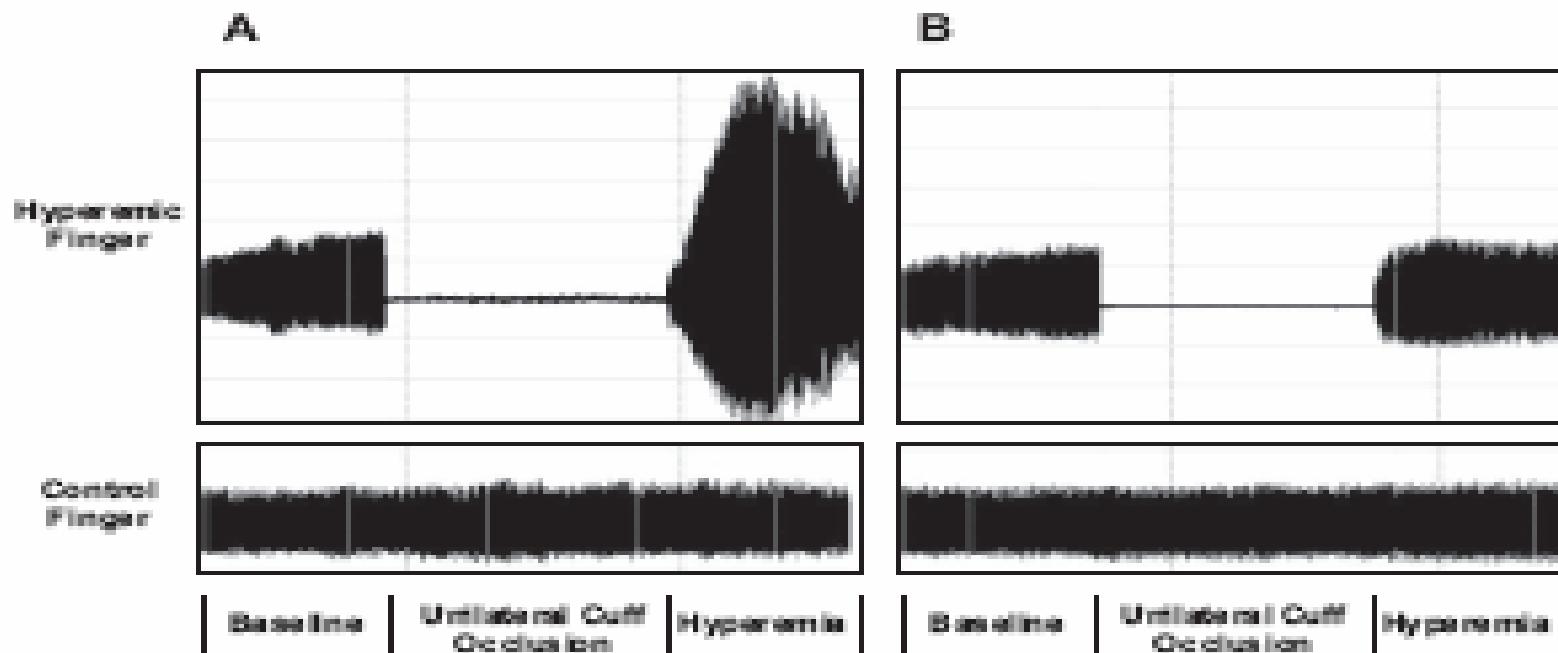
## Dos semanas



# **ENDO- PAT 2000**





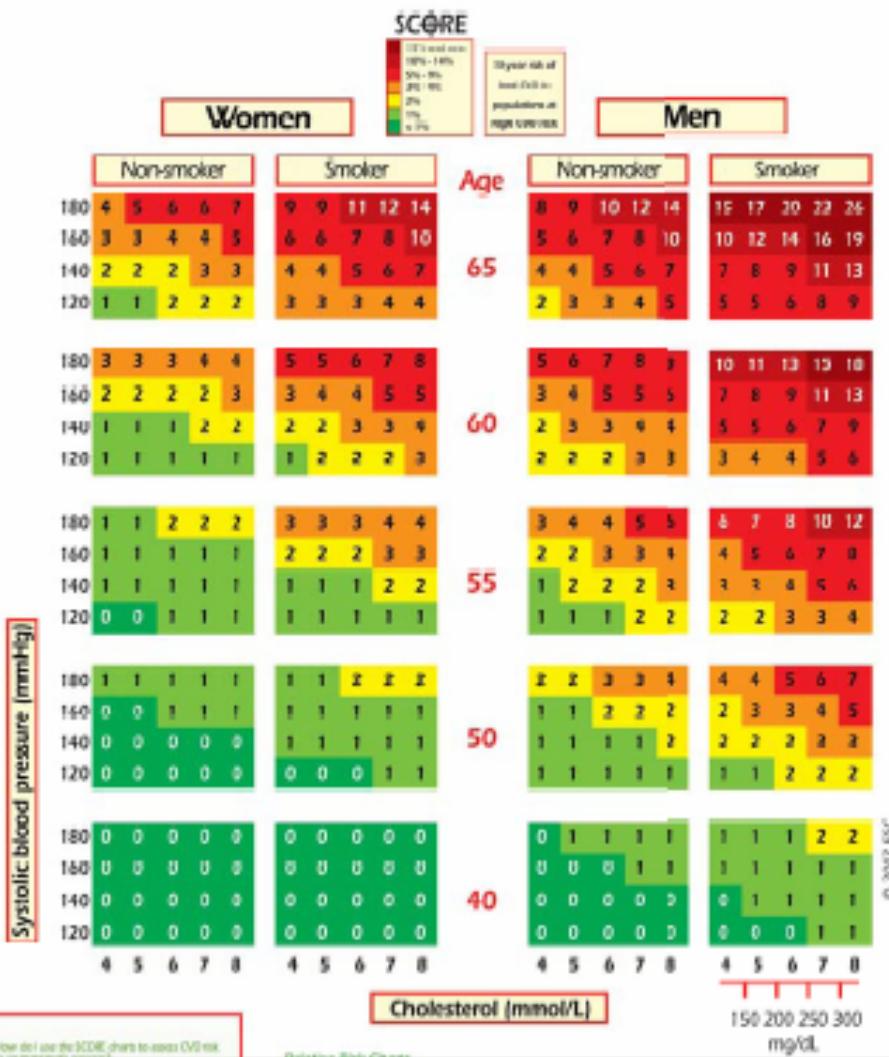


# *Función endotelial:*

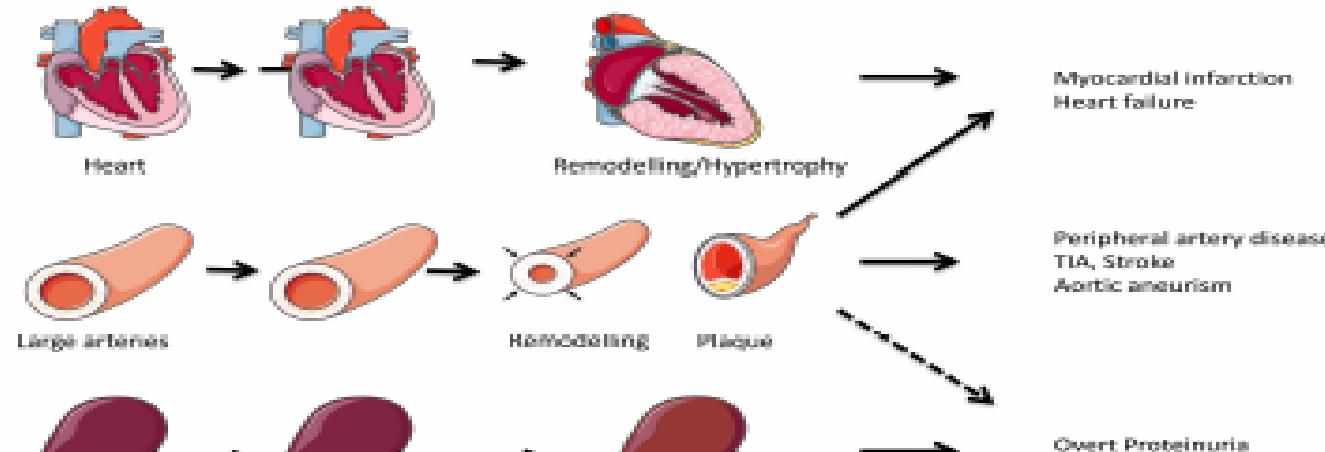
## *¿a quién?*

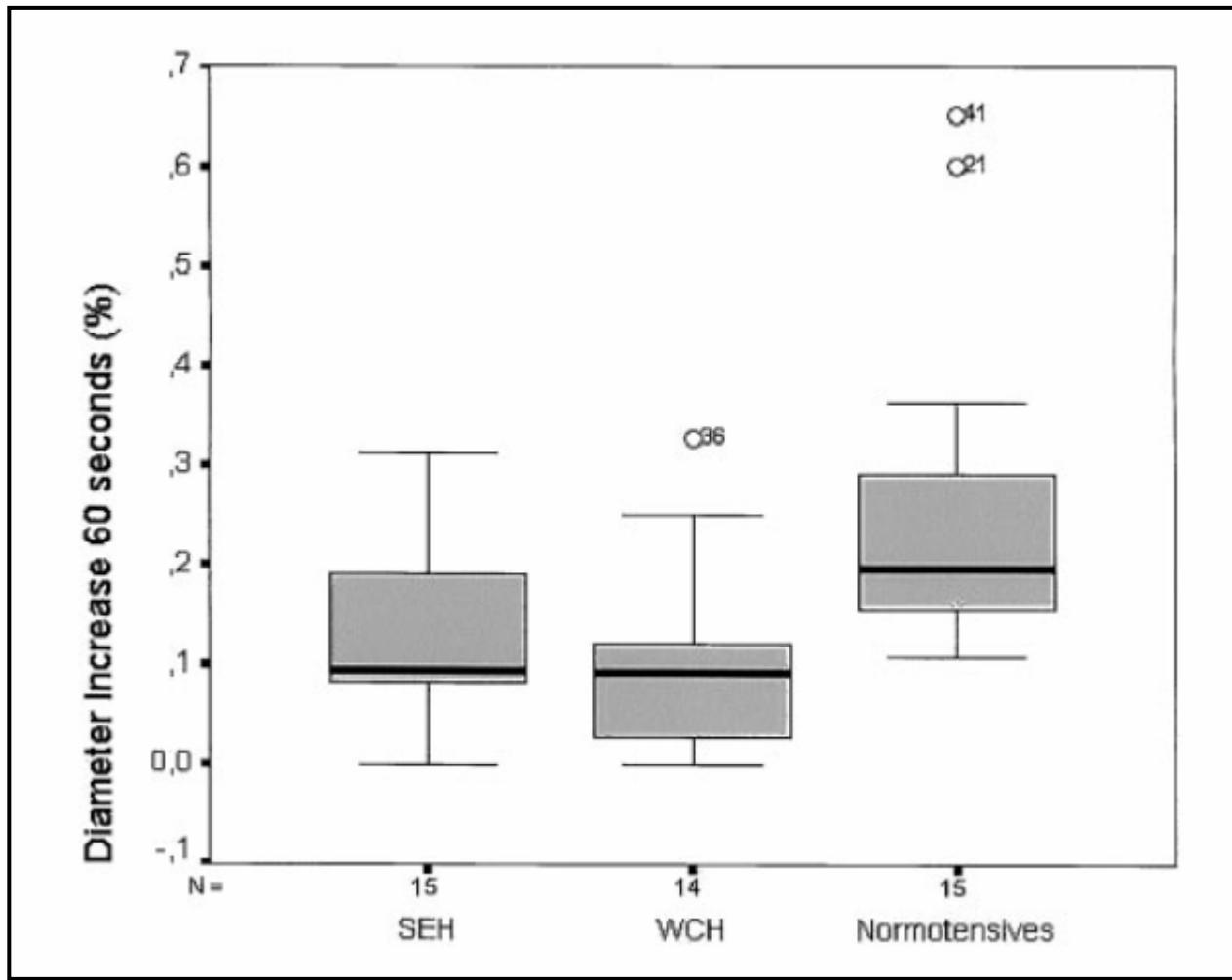
# SCORE - European Low Risk Chart

10 year risk of fatal CVD in low risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status

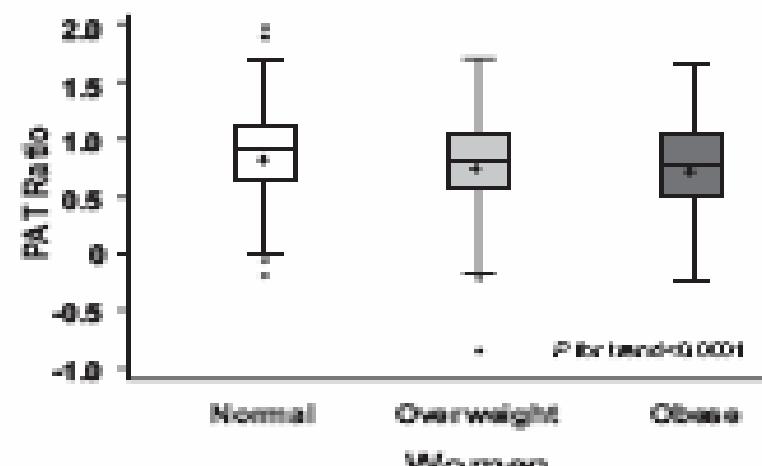
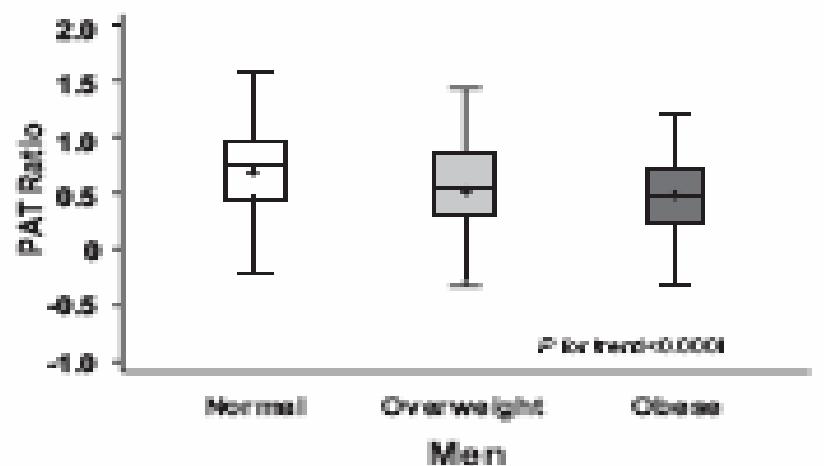
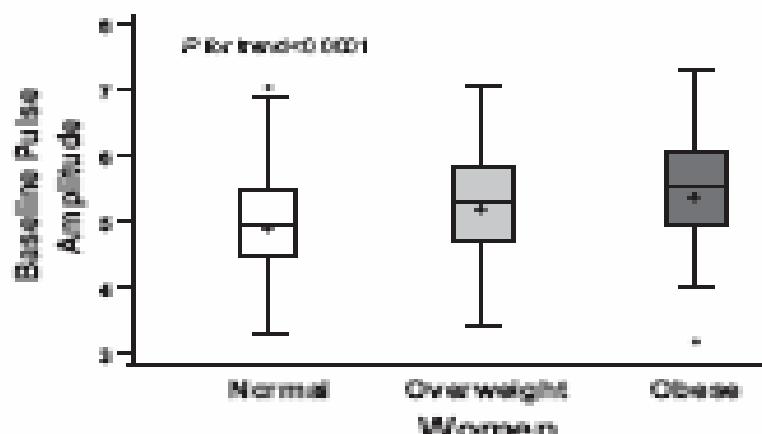
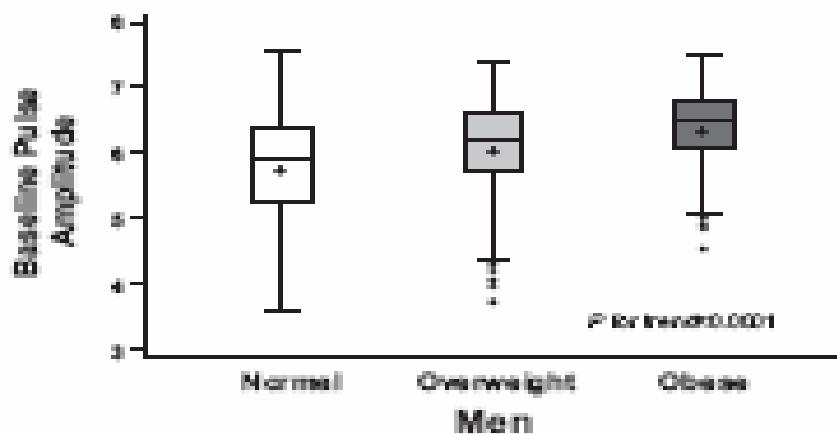


### Endothelial dysfunction and cardiovascular disease





**¿Es la FMD un predictor de  
eventos cardiovasculares?**



**TABLE 2**  
**Studies demonstrating a relationship between endothelial function and prognosis**

Author	Patient population	Conclusions
<b>Coronary vasomotion</b>		
Al Suwaidi et al (38)	Mild coronary atherosclerosis (n=157)	Predictive of increased rates of myocardial events
Schachinger et al (49)	Chest pain (n=147)	Independently predictive of increased rates of myocardial events
Hollenberg et al (59)	Postcardiac transplant (n=73)	Predictive of CV events
Halcox et al (60)	Patients with and without CAD (n=308)	Independent predictor of CV events
Targonski et al (81)	Patients with mild CAD (n=503)	Independent predictor of cerebrovascular events
<b>Impedance plethysmography</b>		
Perticone et al (14)	Untreated hypertensives (n=225)	Predictive of increased rates of myocardial events in step-wise modelling
Heitzer et al (42)	Patients with CAD (n=281)	Independent predictor of CV events
Fichtlscherer et al (62)	Patients with ACS (n=198)	Response to acetylcholine predictive of events
<b>Flow-mediated dilation</b>		
Modena et al (10)	Post-menopausal female hypertensives (n=400)	Lack of improvement in endothelial dysfunction with antihypertensives associated with CV events
Rossi et al (15)	Postmenopausal women (n=2264)	FMD predictive of CV events beyond traditional risk factors
Yeboah et al (51)	Elderly cohort (n=2792)	FMD predictive of CV events beyond traditional risk factors
Gokce et al (63)	Elective vascular surgery patients (n=187)	FMD independently predictive of CV events
Brevetti et al (64)	Patients with peripheral vascular disease (n=131)	ABI predictive of CV events
Chan et al (65)	Patients in cardiac rehabilitation (n=152)	FMD associated with CV events
Karatzis et al (66)	Patients with NSTEMI (n=98)	FMD independently predictive of CV events
Patti et al (17)	Patients postcoronary stent (n=136)	FMD predictive of restenosis
Shimbo et al (52)	Multiethnic population with varied levels of risk (n=842)	FMD predictive of outcomes, but not in multivariate analysis
<b>Reactive hyperemia</b>		
Huang et al (18)	Vascular surgery patients (n=267)	RH and FMD independently predictive of CV events beyond traditional risk factors

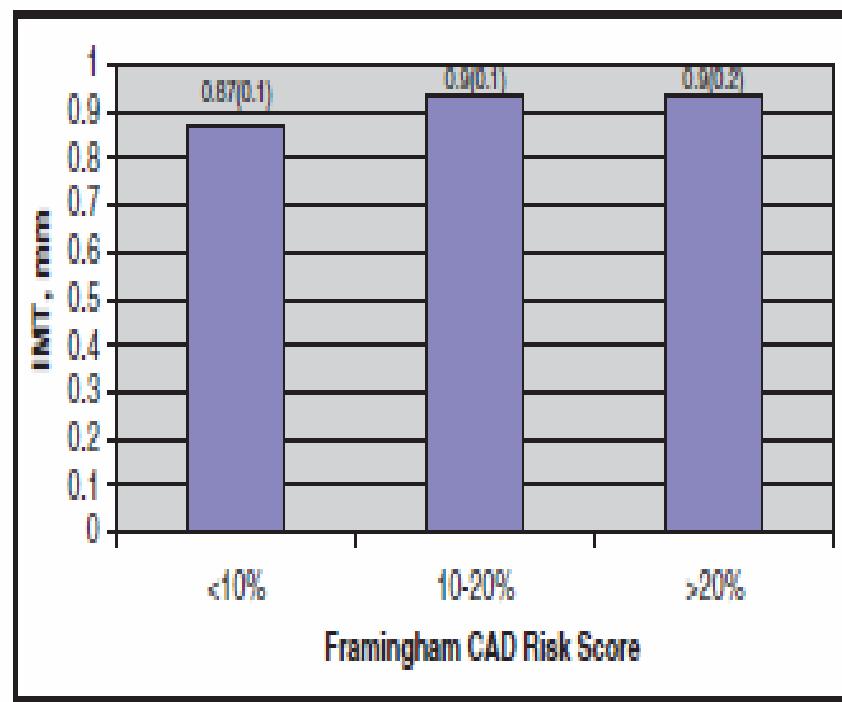
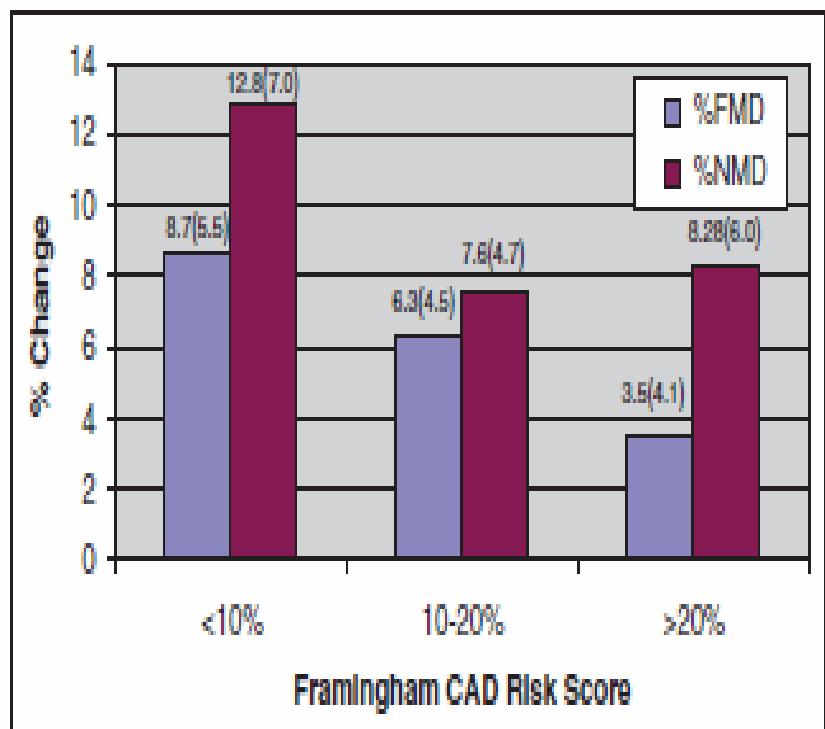
Table adapted from Mancini (58). ABI Ankle-brachial index; ACS Acute coronary syndrome; CAD Coronary artery disease; CV Cardiovascular; FMD Flow-mediated dilation; NSTEMI Non-ST elevation myocardial infarction; RH Reactive hyperemia

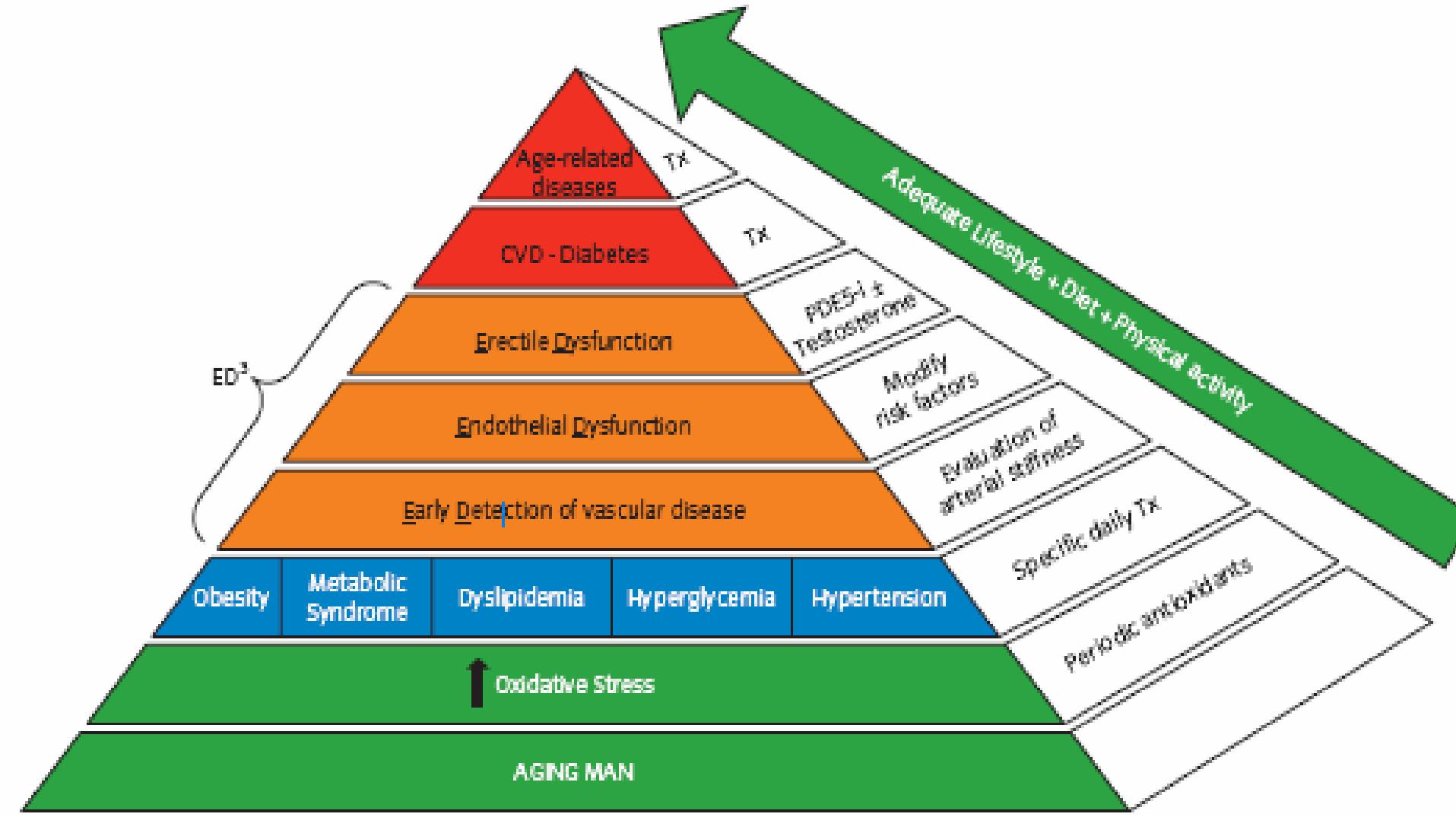
Original Paper

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## The Relationship Between Flow-Mediated Dilatation of the Brachial Artery and Intima-Media Thickness of the Carotid Artery to Framingham Risk Scores in Older African Americans

John Kwagyan, PhD; Saifudin Hussein, MD; Shichen Xu, MD;  
Muluemebet Ketete, MD; Abid R. Maqbool, MD; Robert H. Schneider, MD;  
Otelio S. Randall, MD





## Cross-Sectional Relations of Digital Vascular Function to Cardiovascular Risk Factors in the Framingham Heart Study

- 2008;117:2467-2474.

# **Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events**

**Ronen Rubinshtein<sup>1</sup>, Jeffrey T. Kuvvin<sup>2</sup>, Morgan Soffler<sup>2</sup>, Ryan J. Lennon<sup>3</sup>, Shahar Lavi<sup>1</sup>,  
Rebecca E. Nelson<sup>1</sup>, Geralyn M. Pumper<sup>1</sup>, Lilach O. Lerman<sup>4</sup>, and Amir Lerman<sup>1\*</sup>**

<sup>1</sup>Division of Cardiovascular Diseases, Center of Coronary Physiology and Imaging, Mayo College of Medicine, MB4 523, 200 First Street SW, Rochester, MN 55905, USA; <sup>2</sup>Division of Cardiology, Tufts Medical Center, Boston, MA, USA; <sup>3</sup>Division of Biomedical Statistics and Informatics, Mayo College of Medicine, Rochester, MN, USA; and <sup>4</sup>Division of Nephrology and Hypertension, Mayo College of Medicine, Rochester, MN, USA

Received 11 May 2009; revised 2 November 2009; accepted 22 December 2009; online publish-ahead-of-print 24 February 2010

**Table 2** Estimated 7 years clinical cardiac adverse event rates in patients undergoing reactive hyperaemia–peripheral arterial tonometry in relation to natural logarithmic scaled reactive hyperaemia index

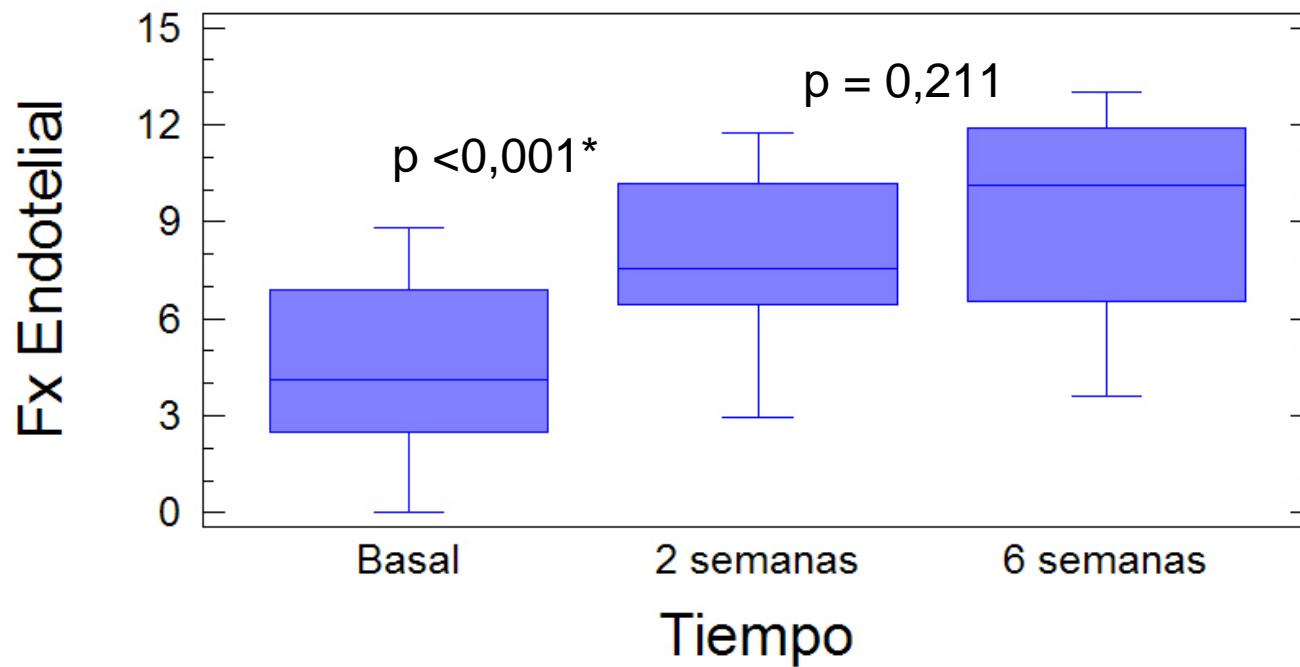
Parameter	Patients with L_RHI < 0.4 (n = 130)	Patients with L_RHI ≥ 0.4 (n = 140)	HR (95% CI)	P-value
CV death	3.9%	0.0%	∞ (1.32, ∞)	0.032
Myocardial infarction	3.4%	3.7%	1.06 (0.27, 4.27)	0.93
Revascularization	12.7%	11.4%	1.21 (0.55, 2.65)	0.64
Stroke	5.3%	3.1%	1.6 (0.45, 5.68)	0.46
CV hospitalizations	30.5%	18.7%	2.06 (1.26, 3.38)	0.018 <sup>a</sup>
AE	48 %	28%	1.83 (1.18, 2.81)	0.030 <sup>a</sup>

<sup>a</sup>P-values adjusted for the multiple tests done to identify the optimal cut-point.

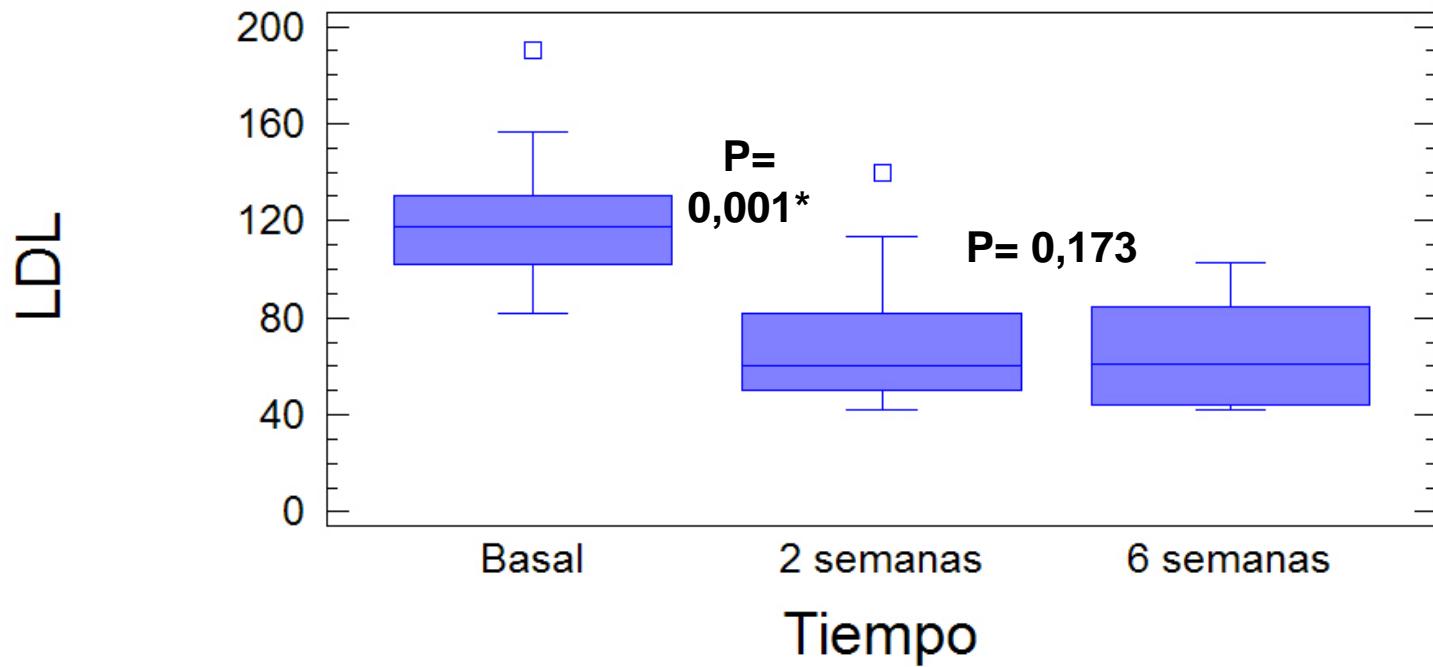
**¿La FMD mejora con el  
tratamiento?**

»Sí

# Función endotelial

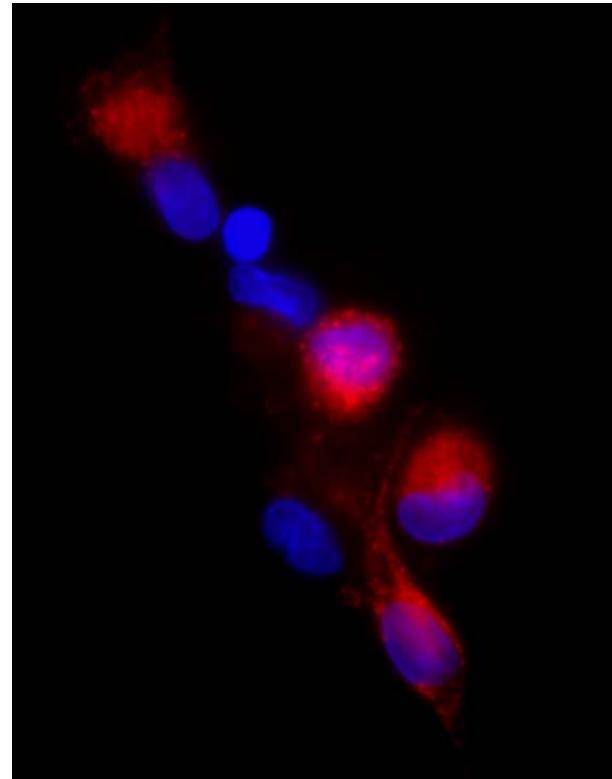
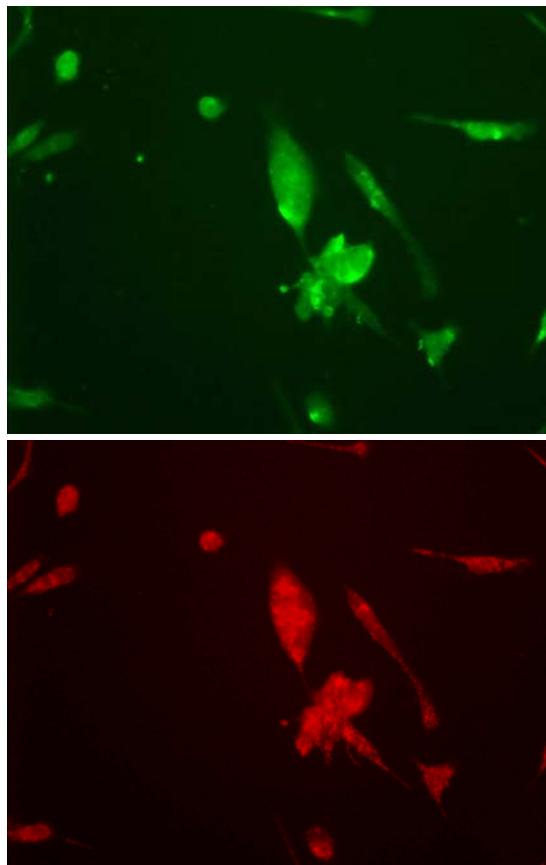


# LDL-colesterol



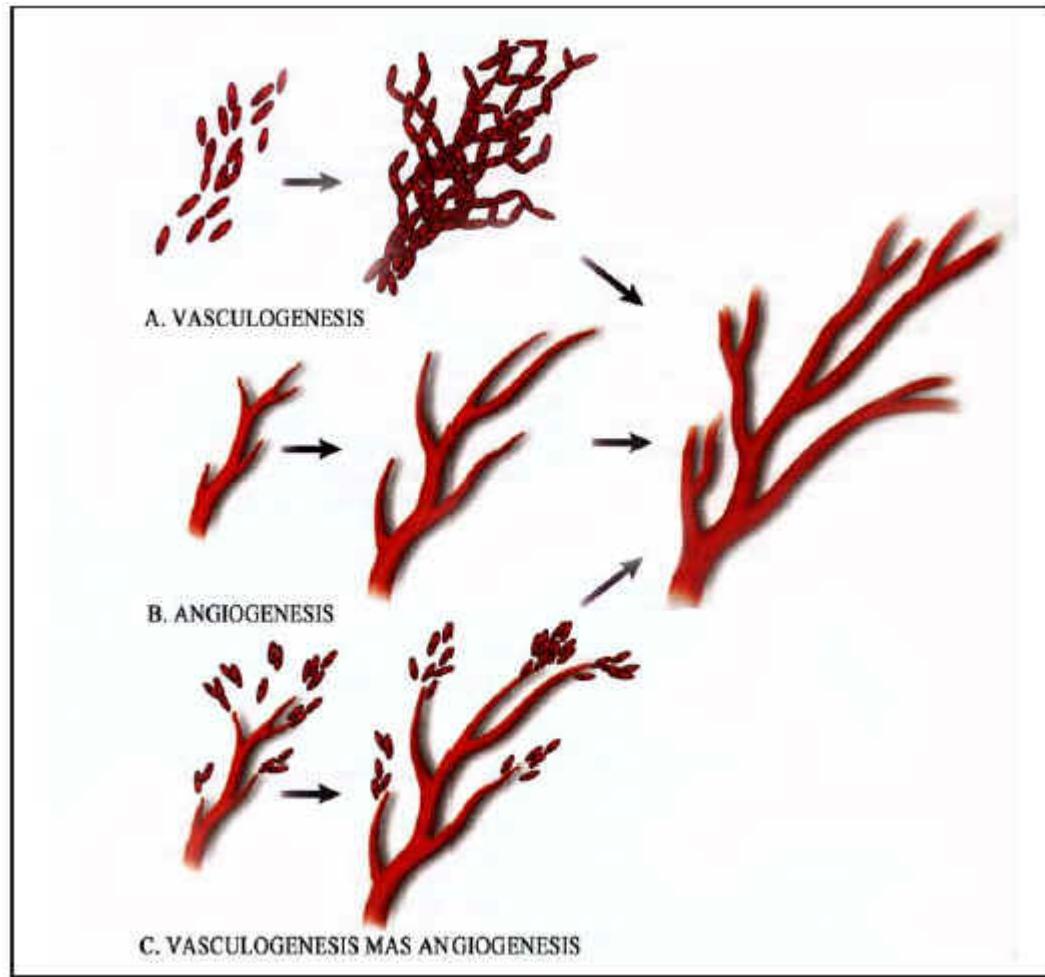
	Basal	2 Semanas	6 Semanas	P
LDL	$119 \pm 26,64$	$71,12 \pm 28,16$	$65,43 \pm 22,17$	< $0,001^*$

# Aislamiento CPE: Cultivo

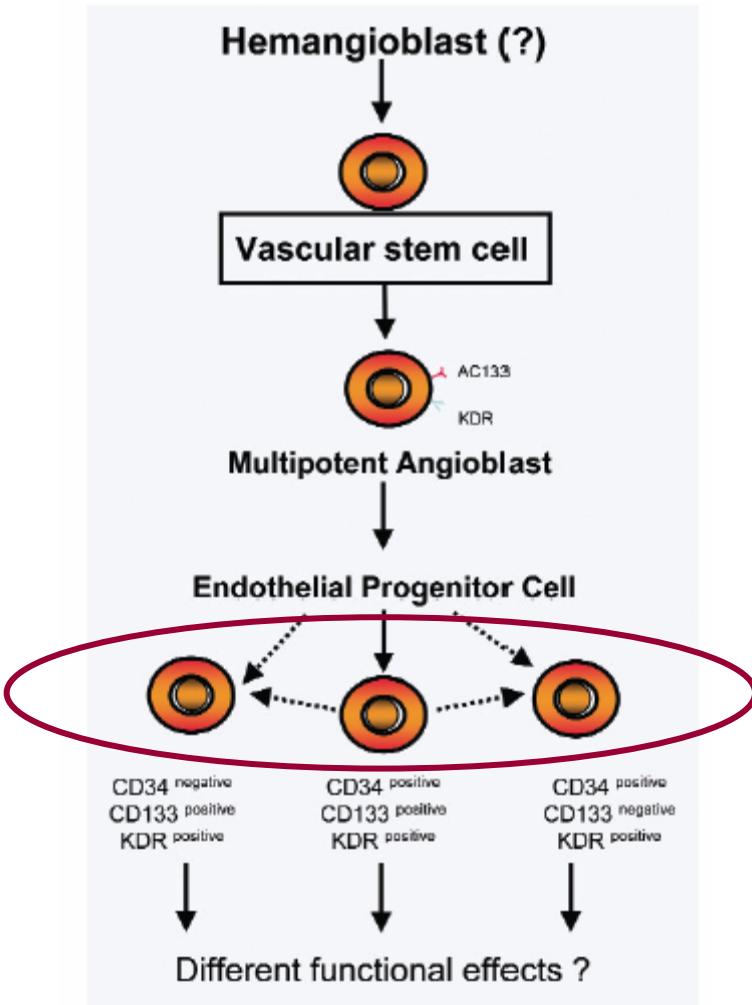


Se utiliza tinción fluorescente para detectar las células que se han marcado con la aglutinina-I del *Ulex europaeus* (UEA-1) y que han incorporado del medio LDL acetiladas, teñidas. Las células con el doble marcaje son consideradas como CPE.

# CÉLULAS PROGENITORAS ENDOTELIALES

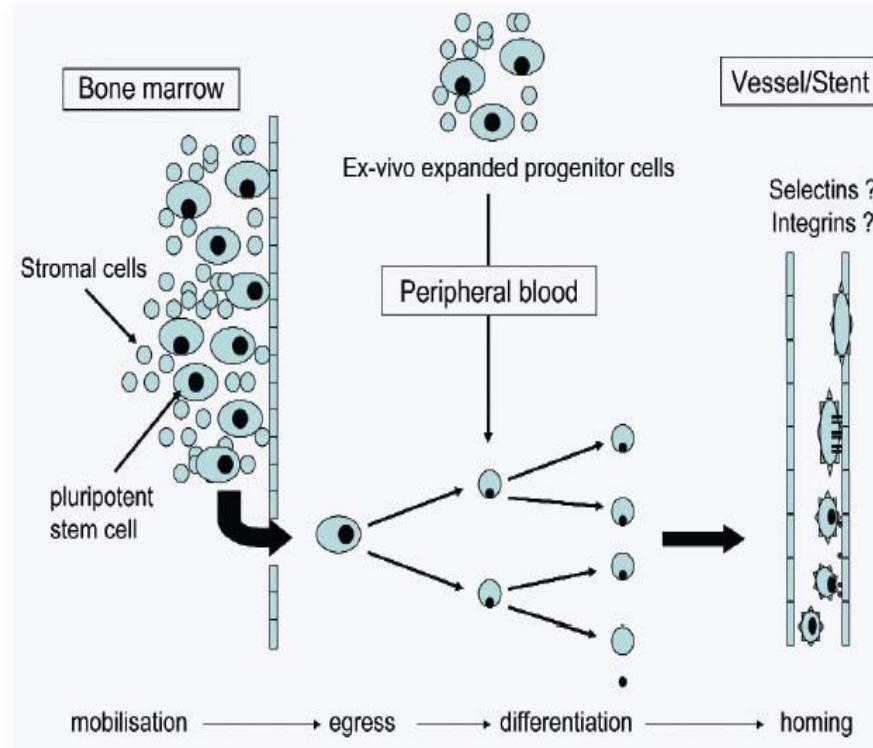


# CPE: Biología



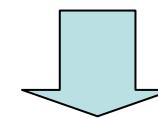
**Pool heterogéneo**  
**Distintos estados madurativos**

# CPE: Función



## FUNCIONES

- Re-endotelización**
- Reparación endotelio dañado**



## FUNCTION ENDOTELIAL

# Factores modificadores CPE

## FACTORES ESTIMULANTES DE LAS CPE

Óxido Nítrico  
Factor de crecimiento del endotelio vascular (VEGF)  
Fármacos:

- o Estrógenos
- o Eritropoyetina
- o Estatinas
- o ARA-II/ IECAs

Eventos isquémicos

## FACTORES INHIBIDORES DE LAS CPE

Edad  
FRCV

- o HTA
- o DL y LDL
- o DM 1 y 2
- o Tabaco

Homocisteína

# CPE

	Basal	2 semanas	6 semanas	P
<b>Cultivo (nº)</b>	$18,88 \pm 31,93$	$27,11 \pm 35,9$	$89,23 \pm 114,55$	$p = 0,02^*$
<b>Citometría (%)</b>	$0,11 \pm 0,09$	$0,048 \pm 0,031$	$0,053 \pm 0,019$	$p = 0,368$

# ¿Es la resolución de la DE clínicamente relevante ?

1. Antioxidantes
2. Biopterina
3. Reducción peso y sal
4. Ejercicio

- Calcio antagonistas
- B Bloqueantes
- ARA II-IECA-Aliskiren
- Estatinas
- EPO